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REVIEW

Buccal midazolam for pediatric convulsive seizures: efficacy, safety, and patient acceptability

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Abstract: Prolonged seizures and status epilepticus are a common acute neurological presentation in pediatric practice. As a result, there is a need for effective and safe medications that can be delivered to convulsing children to effect rapid seizure termination both in hospital and community settings. The challenges of achieving intravenous access, particularly in young children, mandate alternative routes of administration for these drugs. Over the last ten years, midazolam delivered via the buccal mucosa has been demonstrated to be efficacious, safe, and acceptable to children and their caregivers, and a formulation has recently been licensed for use in Europe. The aim of this article is to review the clinical pharmacology with respect to these issues.

Keywords: pediatrics, neurology, pharmacology, buccal midazolam

Introduction

Prolonged seizures are a common problem in both adult and pediatric practice. While the classical definition of status epilepticus encompasses seizure activity lasting 30 minutes or more, or a series of seizures without recovery of consciousness between them, it is widely agreed that treatment to effect termination should not be delayed. The longer a seizure endures, the more likely the development of pharmacoresistance,[1] and animal studies would suggest a greater likelihood of neuronal damage.[2] As a result, an operational definition of a seizure or intermittent seizures without full recovery of consciousness lasting more than 5 minutes is used as a guide for intervention.[3]

Population-based studies of the incidence of status epilepticus in the developed world estimate an incidence of 10–20 per 100,000 individuals per year in the adult population, with the incidence rising with age.[4] Only two studies have attempted to determine the incidence in children, with results of 10.9 cases per 100,000 per year in Switzerland,[5] and more recently an estimate of 17–23 cases per 100,000 per year in North London, UK.[6] This latter study showed an age predominance in the first four years of life, with a recurrence rate of 17% in one year. These studies of status epilepticus used the classical definition and therefore underestimate the true incidence and burden of prolonged seizures requiring treatment as delineated above. In addition, the incidence is likely to be significantly higher in areas where malaria is endemic, with cerebral malaria being a common cause of prolonged seizures.[7]

The association of seizure duration with increased pharmacoresistance to termination underlines the need for effective therapy to be given early in the time course. This mandates an agent that can be safely administered outside the health care environment

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by caregivers or primary responders. The ideal drug for such a purpose would have the following characteristics:

- rapid onset of action
- broad spectrum of efficacy, ie, not restricted to a particular seizure type or underlying cause
- prolonged duration of action
- minimal adverse effects
- simple and socially acceptable administration route for both patient and caregiver
- easy storage and portability.

Benzodiazepines have been used for the management of acute seizures and epilepsy since the 1960s and are, at present, the drugs of first choice for status epilepticus and prolonged seizures in both adults and children.[8] The benzodiazepines share a common set of neuropharmacological effects, including anxiolysis, sedation, muscle relaxation, and anticonvulsant action. The differing affinity of each of the benzodiazepines for their receptor subtypes account for the extent to which they exert each of these effects. In general, the benzodiazepines, diazepam, lorazepam, and midazolam, have been the most studied and are therefore preferred for the acute management of seizures.

For a significant period of time, diazepam, administered rectally, has been the treatment of choice for effecting the cessation of prolonged or serial seizures in the community. However, the requirement for rectal delivery represents a significant barrier to its use. From the patient's perspective, it adds the need for exposure of intimate anatomy to the potential embarrassment of suffering a seizure. There is a similar concern from a caregiver's point of view allied to the fact that the route is not particularly accessible, particularly for larger adults, leading to a reluctance to give the drug. In addition, people administering rectal diazepam may be concerned that they are placing themselves at risk of allegations of sexual abuse.[9] As a result, over the past 10 years, midazolam delivered into the buccal cavity has been growing in popularity and is now the preferred drug for this indication in the UK.[8] The aim of this article is to review the pharmacology, utility, and acceptability of buccal midazolam in relation to its use for acute seizure control.

Buccal route

Systemic delivery of drugs via the buccal or sublingual mucosa in emergency situations is not a recent development. The effect of sublingual administration of nitroglycerin for the relief of cardiac chest pain was described as early as 1957.[10] The route has subsequently merited particular study due to its potential for high patient compliance and unique physiological features.

The buccal mucosa has a large surface area (estimated 50 cm^2) and a relatively porous epithelial membrane, even compared with other mucosal surfaces of the mouth. It is highly vascularized and any drug diffusing across the oral mucosal membranes has direct access to the systemic circulation, bypassing the portal circulation and hence, first-pass metabolism by the liver. In addition, the high rate of blood flow does not present a limiting step to absorption. The buccal mucosa has a lower degree of enzyme expression and activity than the gastrointestinal tract, leading to less drug degradation prior to absorption;[11] the degree of metabolism will, of course, also depend upon the individual drug. Most studies of absorption across the buccal membrane demonstrate that the principal mechanism is passive diffusion across lipid membranes.[12] Table 1 lists some of the potential advantages offered by the buccal route which demonstrate the utility of this route in the emergency situation.

The intranasal route has also been studied in the context of emergency drug administration. It is as accessible as the buccal route and its epithelial membrane is also relatively porous and well vascularized. However, it is limited in that the nasal cavity is of relatively small capacity and is easily flooded by small volumes of drug (approximately 200 µL per adult nostril), leading to loss of active drug to respiration. In addition, in young children, the route is often congested by mucus, which may affect absorption.[9]

Basic pharmacology

Midazolam exerts its action by interacting reversibly with the benzodiazepine binding site of the γ-aminobutyric acid receptor subtype A ($GABA_A$). These are pentameric transmembrane ligand-gated chloride ion channels distributed throughout the neuronal membranes of the central nervous system. Binding of GABA to the receptor results in an inhibitory effect on neurotransmitter release, and when activated by GABA, the $GABA_A$ receptor allows influx of chloride ions, causing hyperpolarization of the neuron membrane.

Benzodiazepines do not bind to the same site as GABA, but to a distinct alternative site. This results in positive allosteric

Table 1 Potential advantages of the buccal route of drug delivery

Advantage	Effect
Rapid absorption	Fast onset of therapeutic effect
Circumvention of portal circulation	No first-pass hepatic metabolism
Circumvention of intestinal absorption	No gastrointestinal enzyme degradation
Noninvasive	Reduced risk of infection
Easily accessible and socially acceptable	Increased compliance

modulation of the receptor, resulting in an increased affinity for GABA, leading to increased frequency of opening of the chloride channel and thereby an enhanced inhibitory action. This explains the anticonvulsant action of benzodiazepines.

Midazolam is metabolized primarily by the cytochrome P450 (CYP) 3A4 isoenzyme. This enzyme is expressed primarily in the liver, but is also active in the intestinal mucosa. As a result, the oral bioavailability of midazolam is only approximately 40%. The unconjugated metabolite, α-hydroxymidazolam, is also pharmacologically active and contributes about 10% of the pharmacological effect of midazolam. The glucuroconjugated α-hydroxymidazolam is excreted in urine, with a terminal elimination half-life of about one hour. Due to the almost exclusive metabolism mediated by the CYP3A4 isoenzyme, coadministration of CYP3A4 inhibitors and inducers may result in pharmacokinetic interactions. CYP3A4 is only expressed at low levels in the liver in the neonatal period, increasing to adult levels over the first year of life. Consequently, young infants may experience more prolonged effects, both desirable and undesirable, and repeated dosing may lead to accumulation.[3]

The characteristic undesirable effects of benzodiazepines are reported also for midazolam. Sedation, amnesia, impaired attention, and impaired muscular function may adversely affect the ability to drive or use machines. Paradoxical reaction such as agitation, involuntary movements, hyperactivity, hostility, rage reactions, aggressiveness, excitement, and assault have been reported. These reactions occur mainly with high doses and/or when the injection is given rapidly. The highest risk for paradoxical reaction has been reported for children and elderly patients, as well as patients with actual or amnestic psychiatric diseases and patients with alcohol addiction. Furthermore paradoxical reaction is often related to high midazolam doses.[13]

Midazolam is unique among the benzodiazepines in that its lipophilicity and hydrophilicity is pH-dependent (Figure 1). The alkaline nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form water-soluble salts with acids. Under acidic conditions, midazolam is present as an equilibrium mixture of the closed-ring form and an open-ring structure, formed by the acid catalyzed ring opening of the 4,5-double bond of the diazepine ring. Under physiologic conditions (pH 7.5, 37°C), the open-ring form reverts to the physiologically active, lipophilic, closed-ring form.[14] These physicochemical properties provide significant flexibility for the production of a formulation of midazolam suitable for transmucosal administration when compared with some of the other benzodiazepines. The basic pharmacokinetic parameters of midazolam are summarized in Table 2, and in comparison with diazepam and lorazepam.

Clinical pharmacology

Midazolam, lorazepam, and diazepam have all been studied to a greater or lesser extent following buccal administration, although midazolam more extensively so, particularly in relation to seizure termination.

The pharmacokinetic studies of midazolam and lorazepam (included for comparison) following buccal administration are summarized in Table 3. Diazepam has not been studied in this way. These studies demonstrate that the time taken to reach peak plasma concentrations is significantly lower for midazolam compared with lorazepam. This indicates that it is more likely to achieve therapeutic plasma concentrations, and buccal midazolam is thus more useful than buccal lorazepam

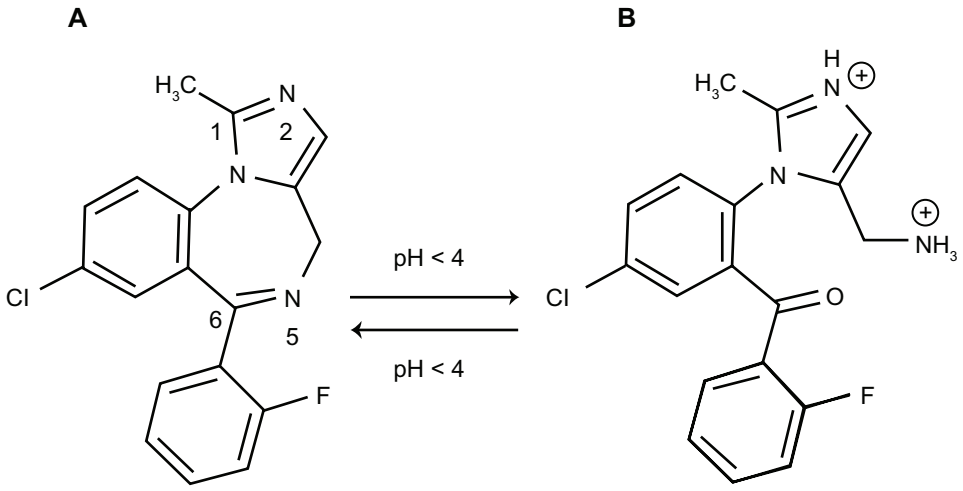

Figure 1 PH-dependent lipo-and hydrophilicity of midazolam.

Table 2 Summary of the pharmacokinetic parameters of the main benzodiazepines used to effect acute seizure termination[15]

	Midazolam	Lorazepam	Diazepam
Oral bioavailability (%)	40	99	100
Volume of distribution (L/kg)	0.8–1.7	0.8–1.3	0.7–1.7
Metabolic pathway	Hydroxylation	Glucuronidation	Demethylation, hydroxylation, glucuronidation
Elimination half-life of parent drug (hours)	1.7–3.5	8–25	20–100
Elimination half-life of major active metabolite (hours)	1.1	NA	30–200

Abbreviation: NA, not applicable.

Table 3 Pharmacokinetic studies of buccal midazolam and lorazepam

Author	Drug	Dose (mg)	Subjects	T_{max} (minutes)	C_{max} (ng/mL)	Comments
Scott et al[16]	Midazolam	10	10 healthy adults	46 ± 28	32.7 ± 3.2	
Schwagmeier et al[17]	Midazolam	5	8 healthy adults	30 (15–90)	55.9 (35.6–77.9)	Bioavailability 74.5%
Muchohi et al[18]	Midazolam	0.3 mg/kg	8 children with malaria	10 (5–40)	186 (64–394)	Bioavailability 87%
Greenblatt et al[19]	Lorazepam	2 mg	10 healthy adults	135	20.7	Sublingual administration
Anderson et al[20]	Lorazepam	2 mg	12 healthy adults	160.9 ± 46.9	14.4 (3.3)	

Abbreviations: T_{max} time to maximum plasma concentration (mean ± standard deviation, range); C_{max}, maximum plasma concentration (mean ± standard deviation, range); IV, intravenous.

Table 4 Summary of comparative trials of buccal midazolam

Author	Patient group	Dose of buccal midazolam	Comparator	Outcome measures
Scott et al[9]	18 children and young people in a UK residential center for severe epilepsy (79 episodes of seizure)	10 mg	Rectal diazepam 10 mg	Seizure termination within 10 minutes of administration
McIntyre et al[21]	177 children and young people (aged 6 months to 16 years) presenting to UK emergency departments (219 episodes of seizure)	2.5 mg (age 6–12 months) 5 mg (age 1–4 years) 7.5 mg (age 5–9 years) 10 mg (age 10 years+)	Rectal diazepam, same dose as midazolam	Seizure termination within 10 minutes of administration
Baysun et al[22]	43 children (aged < 12 years) presenting to a children's emergency department in Turkey	0.25 mg/kg	Rectal diazepam 0.5 mg/kg (age < 5 years) 0.3 mg/kg (age > 5 years)	Seizure termination within 10 minutes of administration
Mpimbaza et al[23]	330 children (aged 3 months to 12 years) presenting to an emergency department in Uganda	2.5 mg (age 6–12 months) 5 mg (age 1–4 years) 7.5 mg (age 5–9 years) 10 mg (age 10 years+)	Rectal diazepam, same dose as midazolam	Seizure termination within 10 minutes of administration
Talukdar and Chakrabarty[24]	120 children (aged < 12 years) presenting to an emergency department in India	0.2 mg/kg	Intravenous diazepam 0.3 mg/kg	Seizure termination within 5 minutes of administration
Ashrafi et al[25]	98 children (aged 3 months to 12 years) presenting to the emergency departments of two Iranian hospitals	0.3–0.5 mg/kg	Rectal diazepam 0.5 mg · kg	Seizure termination within 5 minutes of administration Buccal midazolam as effective as rectal diazepam
Nakken and Lossius[26]	22 adults in a Norwegian residential center for severe epilepsy (80 episodes of seizure)	10–20 mg	Rectal diazepam 10–30 mg	Seizure termination within 10 minutes of administration

for the treatment of acute seizures where rapid termination is desirable. However, extension of these data to the clinical situation is fraught. A minimum effective plasma concentration at which each of the benzodiazepines effects its anticonvulsant action has not been defined. This is likely to be due to the significant variation between individuals and cause of seizure.

Efficacy studies

Virtually all of the prospective randomized and quasi-randomized controlled trial data relating to treatment of prolonged seizures with buccal midazolam have been collected from studies of children and adolescents. These data are summarized in Table 4. Five studies compared its efficacy against that of rectal diazepam. In all of these, buccal midazolam was found to be as effective or more effective. In one study,[24] efficacy was compared with intravenous diazepam, and observed that time to seizure termination following drug administration was shorter with intravenous diazepam, but that once the time to achieve intravenous access was accounted for, the mean time elapsed between noticing seizure activity and its control was significantly less for buccal midazolam. Therefore, there is a significant body of evidence supporting buccal midazolam as first-line therapy for prolonged seizures, where intravenous drug administration is not possible or practical.

Safety

The major safety concern regarding administration of benzodiazepines to children experiencing a prolonged seizure is the risk of respiratory depression, especially if it should occur outside of hospital. Respiratory depression was reported in two of the comparative trials listed in Table 4, with an incidence of 0.6%–5%. This was not increased compared with that seen in the diazepam-treated groups.

As a result, there have been suggestions that a test dose of buccal midazolam should be given to children in hospital prior to its use in the community.[27] However, a dose given to a conscious, nonconvulsing child does not mimic its use during a seizure, and most clinicians do not follow this practice.[28]

Key findings	Trial conclusion	Comments
Buccal midazolam: 75% of seizures responded (30 of 40 episodes) Rectal diazepam: 59 % of seizures responded (23 of 39 episodes, $P = 0.016$)	Buccal midazolam is as effective as rectal diazepam	Small sample size Two patients accounted for nearly 50% of the seizure episodes No adverse cardiorespiratory effects were recorded
Buccal midazolam: 56% of seizures responded (61 out of 109 episodes) Rectal diazepam: 27% of seizures responded (30 out of 110 episodes) $P < 0.001$	Buccal midazolam more effective than rectal diazepam	5 children in buccal midazolam arm and 7 children in rectal diazepam arm experienced respiratory depression
Buccal midazolam: 78% of seizures responded (18 out of 23 patients) Rectal diazepam: 85% of seizures responded (17 out of 20 patients, $P > 0.05$)	Buccal midazolam as effective as rectal diazepam	Small sample size 1 child in rectal diazepam group experienced respiratory depression
Buccal midazolam: 69.7% of seizures responded (115 of 165 patients) Rectal diazepam: 57% of seizures responded (94 of 165 patients, $P = 0.016$)	Buccal midazolam more effective than rectal diazepam	Malaria the most common cause for seizures (67.3% of patients) 2 patients in each group experienced respiratory depression
Buccal midazolam: 85% of seizures responded (51 of 60 patients); Intravenous diazepam: 93.3% of seizures responded (56 of 60 patients, $P = 0.142$)	Buccal midazolam as effective as intravenous diazepam	No adverse cardiorespiratory effects recorded
Buccal midazolam: 100% of seizures responded (49 out of 49 patients) Rectal diazepam 82% of seizures responded (40 of 49 patients, $P < 0.001$)	Buccal midazolam as effective as rectal diazepam	No adverse cardiorespiratory effects recorded
Buccal midazolam: 74.4% of seizures responded (32 of 43 episodes) Rectal diazepam: 83.3% of seizures responded (30 of 37 episodes, *P* not significant)	Buccal midazolam as effective as rectal diazepam	Small sample size No adverse cardiorespiratory effects recorded

Open-label prospective and retrospective studies and case reports are also a valuable source of signals of potential adverse effects. Both Kutlu et al[29] and Melendez et al[30] reported no adverse cardiorespiratory effects in their series of patients. There is a single case report of an episode of hypotension following administration of buccal midazolam.[31] An online report of a search of the UK National Health Service National Reporting and Learning System following a signal generated by a event involving respiratory depression in the community attributed to buccal midazolam administration revealed 132 reported medication incidents.[32] Three of these were associated with severe harm and five with moderate harm. Little further information is provided, but it would appear that these events were associated with "wrong dose errors", eg, ten-fold overdosing. As a result, although difficult to quantify accurately, it would appear that the risk of cardiorespiratory compromise as a result of administration of buccal midazolam is acceptably low.

There have been some theoretical concerns regarding the administration of a medication into the mouth of an actively convulsing child with respect to the risk of aspiration. However, the volumes of drug are very small and are likely to be exceeded significantly by the excess saliva produced during a seizure. In practice, these concerns have not materialized as safety issues.

Patient and caregiver acceptability

There has been little formal study of the acceptability of buccal midazolam to both patients and their caregivers. It would seem self-apparent that the buccal route is much preferred over the rectal route, for reasons of ease of administration and obviation of the need to expose intimate body areas. Data from comparative trials are limited but indicate that, where measured, the time required for buccal drug administration is significantly less than for the rectal or intravenous routes. In addition, Ashrafi et al[25] reported that 94% of parents whose children were treated with buccal midazolam were satisfied with the care they had received compared with only 14% of those parents whose children had been treated with rectal diazepam. Nakken and Lossius[26] reported that all nursing staff involved in their trial preferred administering buccal midazolam to rectal diazepam.

A telephone survey of the parents of 53 children who had been prescribed buccal/nasal midazolam was conducted in 2004.[33] Eighty-three percent of families reported it to be effective and easy to use. In addition, of those families who had previously used rectal diazepam, 83% preferred midazolam.

Table 5 Recommended doses for buccal midazolam[35]

Age range	Dose
3 months up to one year	2.5 mg
One year up to 5 years	5 mg
5 years up to 10 years	7.5 mg
10 years up to18 years	10 mg

Licensed status and dose recommendations

Until 2012, midazolam was administered buccally for prolonged seizures on an unlicensed basis. The initial randomized trials[9,21,22] used the intravenous preparation of midazolam. However, solutions of midazolam specifically for buccal use were subsequently developed, although on an unlicensed basis. In particular, Epistatus® (Special Products Ltd, Weybridge, UK) was used in two trials.[25,26] The other trials did not stipulate the formulation of midazolam used. In 2012, Buccolam® (Viropharma, Downingtown, PA) was granted a license by the European Medicines Agency for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children, and adolescents (from 3 months to <18 years).[34] Buccolam has the same formulation as the intravenous preparation but is presented in prefilled syringes for ease of administration. In the US, buccal midazolam does not appear to be used for this indication. The only medication approved by the US Food and Drug Administration for nonintravenous treatment of prolonged seizures is rectal diazepam.

The original dose of buccal midazolam for treating prolonged seizures was 0.3 mg/kg, up to a maximum of 10 mg. However, this has recently been changed to age-defined recommendations, and details of these doses are summarized in Table 5. These are the licensed doses for Buccolam.

Conclusion

There is now a wealth of evidence demonstrating the efficacy of buccal midazolam for the termination of acute prolonged seizures in children. This has been recognized by its inclusion in many national guidelines, and interestingly its extension into adult practice; perhaps one of the few occasions in drug development where children have led the way. As a result, a licensed product is now available in Europe (Buccolam). This product is in receipt of the first Paediatric Use Marketing Authorisation to be granted by the European Medicines Agency.

Work carried out on acceptability to patients supports the *prima facie* view that administration of a drug into the mouth is preferable to administration into the rectal cavity. The development of therapies for use by parents, caregivers, and paramedics to terminate seizures in the community has

significantly improved the quality of life of families and individuals. Buccal midazolam for prolonged seizures is both effective and safe. The buccal route avoids the social stigma of rectal administration, particularly in older children and adults, and it is appropriate that buccal midazolam should be considered the treatment of choice.

Disclosure

The author reports no conflicts of interest in this work.

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